A Population-Based Case-Control Study of Thyroid Cancer[1]

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ABSTRACT—A population-based case-control interview study of thyroid cancer (159 cases and 285 controls) was conducted in Connecticut. Prior radiotherapy to the head or neck was reported by 12% of the cases and 4% of the controls [odds ratio (OR)=2.8; 95% confidence interval = 1.2-6.9]. Risk was inversely related to age at irradiation and was highest among children exposed under age 10. Few persons born after 1945 received prior radiotherapy, consistent with the declining use of radiation to treat benign conditions in the 1950's. Among females the radiogenic risk appeared to be potentiated by the number of subsequent live-births. Other significant risk factors included a history of benign thyroid nodules (OR=33) or goiter (OR=5.6). Miscarriage and multiparty increased risk but only among women who developed thyroid cancer before age 35 years. Consumption of shellfish (a rich source of iodine) seemed to increase the risk of follicular thyroid cancer, whereas consumption of goitrogen-containing vegetables appeared to reduce risk of total thyroid cancer, possibly because of their cruciferous nature. A significantly low risk was observed among persons of English descent, whereas Italian ancestry appeared to increase risk. No significant associations were found with a number of suspected risk factors: diagnostic x-rays, radioactive isotope scans, occupational radiation exposure, tonsillectomy, Jewish ethnicity, alcohol intake, cigarette smoking, oral contraceptives, lactation suppressants, menopausal estrogens, most other common medications, and water source, New associations were suggested for obesity among females (OR=1.5), surgically treated benign breast disease (OR=1.6), use of spironolactone (OR=4.3) or vitamin D supplements (OR=1.8), and a family history of thyroid cancer (OR=5.2). About 9% of the incident thyroid cancers could be attributed to prior head and neck irradiation, 4% to goiter, and 17% to thyroid nodular disease, leaving the etiology of most thyroid cancers yet to be explained.—JNCI 1987; 79:1-12

Ionizing radiation (1-6) is the only well-established cause of thyroid cancer, although other factors have been suspected, such as dietary iodine (7), chemical or dietary goitrogens (8), preexisting benign thyroid disease (6, *9-13*), antecedent breast cancer (*14,15*), TSH (8, *16*), Jewish ethnicity (2, *17)*, tonsillectomy (17), partial thyroidectomy (8), allergy and skin conditions (17), parathyroid adenoma (*18*), alcohol (*19*), dietary calcium and vitamin D (*16*), multiparty (*13,* 20, 21), and some commonly used drugs (22). Genetic determinants play a role in medullary thyroid cancer (23), but familial occurrence of the more common papillary type has been reported infrequently (24–26). Associations between thyroid cancer and radiation exposure (6), thyroid nodules (6, 13), goiter (6, 13), obesity (*21*), oral contraceptives (13, *21*), lactation suppressants (*21*), estrogens (*21*), and parity (6, *13,* 21) have been reported in two recent case-control surveys of females. The role of hormonal factors in thyroid cancer has long been suspected on the basis of higher incidence rates in females than in males and the peak occurrence in females at ages 15-29 when hormonal activity is enhanced (27, 28). To evaluate a wide range of etiologic hypotheses, a population-based, case-control interview study of males and females who developed thyroid cancer in Connecticut was undertaken.

MATERIALS AND METHODS

Between January 1, 1978, and June 30, 1980, 251 persons with thyroid cancer were reported to the Connecticut Tumor Registry. Forty-eight persons were ineligible for study for the following reasons: 37 had died, of whom 8 were diagnosed only at autopsy; 5 were over age 80 at diagnosis; and 6 were diagnosed out of state. Histologic material from 97.1% of the thyroid cancers was reviewed and classified by one of us (V. A. L.). Four cases were reclassified as noncarcinoma and excluded from the analysis. Of the 199 remaining eligible cases, 159 (80%) were interviewed. Reasons for not completing an interview included the following: physician consent was not received (9'%), or the patient refused (3.5%), left Connecticut (4.5%), could not be located (l%), was too ill (0.5%), or did not speak English (1.5%).

ABBREVIATIONS USED: CI=confidence interval; HCFA= Health Care Financing Administration; MLR=multiple logistic regression; OR= odds ratio; PAR=population-attributable risk; SES=socioeconomic status; TSH = thyroid-stimulating hormone

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Two controls were frequency matched to the cases on sex and year of birth, within 5-year categories. Controls were selected from the general population in two ways: random-digit dialing techniques (29) were used for those under age 65, and Medicare rosters were sampled for those over age 65. Of 1,271 residential phone numbers dialed at random, household censuses were completed on 83.4% of those contacted and 79% of all numbers dialed. The census was conducted by an interviewer who called each number and recorded the age and sex of each household member. The average household refusal rate of 13.5% was similar for urban and rural areas but was slightly higher for extremely small towns and large cities. A census was not possible for 3.2% of households due to language problems. Among 334 persons under age 65 who were approached for an interview, 261 (or 78%) consented, reducing the overall response rate to 62%. Interviews were not obtained if the control refused (16%), had left Connecticut (1%), could not be located (2.5%), was too ill (0.5%), or did not speak English (2%).

Controls aged 65-79 years were chosen from a 1% random sample of Connecticut residents who were Medicare recipients and listed by HCFA. Medicare files enumerate approximately 95-98% of persons over age 65 in the United States (30). Thirty-six controls over age 65 were selected, and 24 (67%) participated. Interviews were not obtained if the control refused (22%), could not be located (2.5%), was too ill (6%), or did not speak English (2.5%). Overall, the nonresponse rate among cases and controls was similar for males and females. Nonrespondents with thyroid cancer were most likely to be males over age 65 years, nonwhite, and single.

Between August and December 1981, 159 cases and 285 controls were interviewed in their homes by trained interviewers (table 1). The questionnaire included items on suspected risk factors for thyroid cancer (e. g., radiation, dietary goitrogens, benign thyroid disease, and medications), general environmental factors (e.g., residence, source of drinking water, usual occupation, and diet), reproductive history for females (e.g., No. of livebirths), and medical history (e.g., illnesses, surgeries, and family occurrences of cancer). Respondents also were asked to classify current and past consumption of 12 food items into the following categories: never, few times a year, few times a month, few times a week, or daily. The average length of the interview was longer for females than for males (40 vs. 30 min) because of the additional questions on reproductive histories, but the interview length did not differ between cases and controls. Dates of exposures were collected for all therapeutic and diagnostic radiation procedures except chest and dental examinations and a few others for which large numbers precluded such detail.

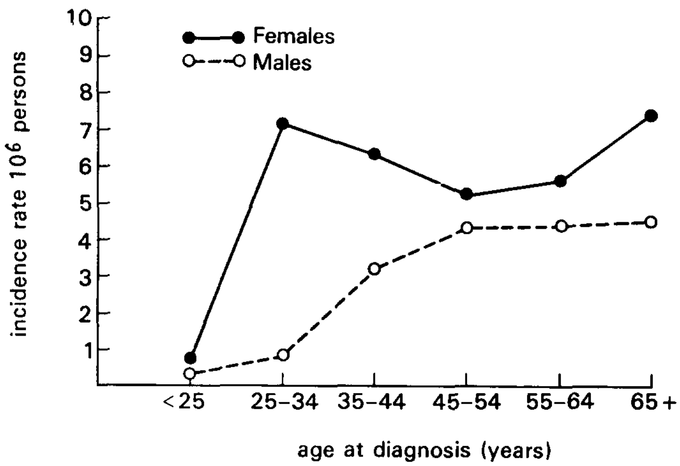
ORS were used as the measure of association between suspected risk factors and thyroid cancer. Maximum likelihood estimates of the OR, adjusted for potential confounding variables, and 95% CIs were computed (32). Significant differences between ORS were tested by a heterogeneity chi square (32). Tests for linear trend over categorical exposure levels were performed and one-sided P-values presented (33). The PAR, i.e., the proportion of thyroid cancers attributable to the exposure under study, was estimated following the method of Cole and MacMahon (34). Linear logistic regression also was used to examine the effects of each risk factor while simultaneously controlling for the other main variables of interest (35). All analyses were done for papillary (including papillary-follicular variants) and follicular cancer separately, but usually other cell types were not distinguished because of the small numbers involved. Data for all thyroid cancers are presented unless results differed by histologic type.

Because this was not a matched case-control study, the selection of an equivalent "age" of the controls to use in the age-adjustment analyses was not straightforward. Adjustment for age at interview would be misleading because thyroid cancers were diagnosed up to 3 years prior to interview and events after diagnosis obviously could be not be related to the prior disease. Unless some equivalent "diagnosis" date was selected for controls, they would always be slightly older than the cases at diagnosis, and bias could result. Therefore, we chose to use the age the controls had reached at the midpoint of the interval from which the thyroid cancers were diagnosed, i.e., April 1, 1979. To exclude exposures that might have been associated with the treatment of disease, or with medical surveillance, we excluded reports of thyroid and other diseases and most radiation ex-

TABLE 1.—*Distribution of interviewed thyroid cancer cases and controls, by age and sex*

Age at diagnosis, yr	Cases				Controls[a]			
	Female		Male		Female		Male	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
<25	4	3.7	2	4.0	20	9.6	4	5.3
25-34	34	31.2	5	10.0	65	31.1	11	14.5
35-44	25	22.9	13	26.0	43[b]	20.6	18	23.7
45-54	14	12.8	16	32.0	40	19.1	22	28.9
55-64	15	13.8	9	18.0	23	11.0	17	22.4
65-79	17	15.6	5	10.0	18	8.6	4	5.3
Total	109	100.0	50	100.0	209	100.0	76	100.0

[a] Equivalent age for controls, i.e., age at midpoint of case ascertainment (April 1, 1979).
[b] One female control was excluded from all subsequent analyses, because her questionnaire appeared to be unreliable.



TEXT-FIGURE 1.—Age-specific thyroid cancer incidence rates per 100,000 for males and females, Connecticut, January 1978–June 1980.

posures that occurred within 2 years of the diagnosis of thyroid cancer for the cases and after 1978 for the controls.

RESULTS

Incidence

During the 2½-year study period, thyroid cancer was reported for 76 male and 169 female Connecticut residents and 6 nonresidents. Thyroid cancer in 4 females was reclassified as benign, leaving 165 for further analyses. The annual incidence rates were 2.0 and 4.1 per 100,000 persons for males and females, respectively. The age-specific incidence rates varied considerably by sex, with the female excess mainly under age 45 (text-fig. 1). Incidence also varied by cell type, with papillary tumors accounting for most cases (65%). The remaining cell types were papillary follicular variants (7.6%), follicular (8.0%), medullary (7.2%), anaplastic (3.3%), malignant lymphoma (2.9%), other (5%), and unknown (0.8%). The distribution of histologic types among those interviewed was similar: papillary (70.4%), follicular (9.4%), mixed papillary -follicular (6.9%), medullary (5.7%), anaplastic (0.6%), and other or unknown (6.9%).

Radiation

Twelve percent of the cases and 4% of the controls (table 2) reported a history of radiation treatment to the head and neck (OR=2.8; 95% CI=1.2-6.9). Among cases, the most frequently mentioned indications were enlarged thymus gland (n=5), acne (n=7), and other skin conditions (n=5). Among controls, radiotherapy was given most often for acne (n=4) and hearing problems (n=3). The average time between exposure and cancer diagnosis was 35 years and ranged between 6 and 58 years. Although the OR was greater for males than females, the difference was not statistically significant. Significant risks associated with radiation were found for both papillary and follicular cancers, Exposure under age 10 carried the highest risk of developing thyroid cancer, and risk decreased significantly with increasing age at exposure. The radiation risk was confined to persons whose thyroid cancer was diagnosed after age 35. The PAR varied by birth cohort, i.e., 16, 6, and 3% for those born before 1930, between 1930-1949,

TABLE 2.—*Risk of thyroid cancer associated with prior radiotherapy to head and neck, adjusted for sex, age, thyroid nodules, and goiter*

Variable	No. of cases exposed	No. of controls exposed	OR[a]	P-value for trend or (95% CI)
Prior radiotherapy to head and neck[b]				
No	132	272	1.0[r]	
Yes	19	11	2.8	(1.2–6.9)
Males	8	2	7.6	(1.3–57)
Females	11	9	1.8	(0.6–5.4)
Histologic type[c]				
Papillary	14	11	2.6	(1.0–6.9)
Follicular	3	11	9.0	(1.6–47)
Age at radiotherapy, yr				
<10	5	0	—[d]	
10–19	7	7	1.8	
≥20	7	4	2.8	.015
Age at thyroid cancer diagnosis among exposed, yr				
<35	2	5	0.7	(0.1–5.2)
≥35	17	6	4.6	(1.5–14.0)
Years since radiotherapy				
<20	3	7	0.8	
20–39	12	3	6.2	
≥40	4	1	6.9	.001

[a] r = referent category.
[b] Prior radiation exposure unknown for 8 cases and 2 controls.
[c] One exposed case had medullary carcinoma and 1 had other cell type.
[d] With 0.5 added to each well, OR = 23.

TABLE 3.—*Risk of thyroid cancer associated with parity and prior radiotherapy to head and neck of females, adjusted for age*

Ever parous	Ever exposed to prior radiotherapy			
	No		Yes	
	OR[a]	No. of cases/ No. of controls	OR	No. of cases/ No. of controls
No	1.0[r]	20/63	1.1	2/3
Yes	1.6	78/136	2.7	9/6
95% CI	0.8-3.2		0.6-13	

[a] r = referent category.

and after 1949, respectively. There was some indication that parous women previously exposed to head and neck irradiation had a particularly high risk of thyroid cancer (table 3).

No significant risks were found for chest x-rays, radioactive isotope scans of the thyroid, mammograms, barium enemas, intravenous pyelograms, or orthopedic x-rays (table 4). Significantly low risks were associated with increasing numbers of dental x-rays and upper gastrointestinal series. The pattern of risk by number of chest x-rays was inconsistent but because dates of these procedures were not obtained, it was uncertain how many of these exposures occurred prior to the diagnosis of thyroid cancer.

Thyroid Disease

A history of either goiter (OR= 33.3) or thyroid nodules (OR =5.6), including adenomas, was reported by 14% of the cases as compared to 1% by the controls (table 5). The mean length of time between the diagnosis of thyroid nodules and thyroid cancer was 6.0 years; for goiter, it was 11.6 years. No risk was evident following hypothyroidism or hyperthyroidism, the use of thyroid hormones to treat thyroid disease or other conditions (e.g., weight problems), the use of antithyroid medications, or partial thyroidectomies.

Other Conditions and Drugs

Asthma, hay fever, diabetes, long-term skin conditions, infectious diseases requiring hospitalization, and tonsillectomy and other surgical procedures were not linked to thyroid cancer. Medications taken for nausea, diarrhea, allergy, high blood pressure, and insomnia, as well as antibiotics and steroids, also were not implicated (table 6). Although diuretics as a group were not associated with thyroid cancer. the use of spironolactone

TABLE 4.—*Risk of thyroid cancer associated with diagnostic x-ray and isotope procedures, adjusted for age, sex, prior radiotherapy to head and neck, and thyroid nodules or goiter*

Diagnostic radiation procedure	No. of procedures[a]	No. of cases	No. of controls	OR[b]	P-value for trend or (95% CI)
Upper gastrointestinal series	1	20	43	0.7	
	2	3	17	0.2	
	≥3	4	7	0.7	.02
Barium enema	1	12	32	0.7	
	2	5	12	0.6	
	≥3	5	11	0.7	.88
Intravenous pyelogram	1	7	16	0.7	
	2	1	4	0.5	
	≥3	2	4	1.1	.27
Thyroid scan	1	14	9	1.6	.10
	≥2	5	2	2.5	
Chest x-rays[c]	0–4	48	113	1.0[r]	
	5–9	50	61	1.6	
	10–14	19	42	0.9	
	≥15	36	37	1.7	.09
Dental x-rays[c]	0–4	31	63	1.0[r]	
	5–9	30	44	1.4	
	10–19	50	78	1.1	
	20–29	23	54	0.7	
	≥30	11	26	0.5	.05
Orthopedic x-rays	Any	96	186	0.7	(0.5–1.2)
Pelvis-abdomen	Any	3	7	0.3	(0.01–2.7)
Head-neck	Any	19	48	0.5	(0.4–1.3)
Chest-thorax	Any	8	14	0.6	(0.2–2.1)
Spine	Any	23	47	0.8	(0.5–1.6)
Extremities	Any	80	144	0.9	(0.6–1.4)
Mammogram	Any	24	30	1.8	(0.9–3.6)

[a] Procedures occurring within 2 yr of date of thyroid cancer diagnosis among cases and equivalent date for controls were excluded, except as indicated.
[b] r = referent category: taken as those individuals never having had the radiographic procedure of interest, unless otherwise specified.
[c] Dates of these procedures were not obtained. Results must be interpreted cautiously because some of the procedures among persons who developed thyroid cancer likely were performed because of their disease.

TABLE 5.—*Risk of thyroid cancer associated with the occurrence and treatment of benign thyroid diseases, adjusted for age, sex, and prior radiotherapy to head and neck*

Disease[a] or treatment	No. of cases	No. of controls	OR	95% CI
Thyroid nodules	17	1	33.3	4.5–691
Goiter	7	2	5.6	1.0–41
Hyperthyroidism	4	7	1.1	0.3–4.3
Hypothyroidism	6	17	0.7	0.2–1.8
Partial thyroidectomy[b]	11	3	0.8	0.1–8.8
Thyroid hormone treatment[b]	20	18	0.9	0.4–2.4

[a] Benign thyroid diseases occurring within 2 yr of date of thyroid cancer diagnosis among cases and equivalent time for controls were excluded.
[b] Adjusted also for goiter or thyroid nodules.

was reported by 2 cases and 1 control (OR= 4.3; 95% CI=0.3–122). Previous breast surgery was noted among 14% of the cases and 9% of the controls (OR= 1.6; 95% CI=0.7–3.6). Three controls but no cases reported a prior history of breast cancer.

Four cases and one control reported a sibling or parent with thyroid cancer (OR=5.2), all of the papillary type. Three cases and no controls reported a first-degree relative with kidney cancer, whereas no association was found with family occurrence of breast cancer. For females only, both adolescent and adult obesity were related to an increased risk of thyroid cancer (OR= 1.5), although no consistent trend was found (table 7).

Reproductive and Hormonal Factors

For women age 35 and over, no reproductive or hormonal factor was linked to thyroid cancer (tables 8 and 9). However, for women under age 35, the risk appeared higher among women who had had a miscarriage or a livebirth. A trend for an increased risk of thyroid cancer associated with number of pregnancies and livebirths and older age at menarche also was suggested. Use of oral contraceptives, lactation suppressants, or any estrogens were not significant risk factors. Among younger women, there was a tendency for the risks to be above unity, but among women 35 years of age and over, risks associated with these hormones were less than one.

Diet

Results of the dietary analyses did not vary with regard to past or present food consumption, and thus only past intake of foods is presented (table 10). A decreased risk of thyroid cancer was observed for increased consumption of chicken, beef, bread, and all of the vegetables evaluated; however, none of these reached statistical significance. An increased risk of follicular, but not papillary, thyroid cancer was associated with a frequent diet of shellfish (OR=3.8), which contain large amounts of iodine. Although most vitamin or mineral supplements did not affect risk, a positive association between vitamin D and thyroid cancer was found.

TABLE 6.—*Risk of thyroid cancer associated with various medical conditions and drugs*

Variable[a]	No. of cases	No. of controls	OR[b]	95% CI
Previous breast surgery[c]	15	19	1.6	0.7–3.6
Hysterectomy[c]	17	37	0.8	0.4–1.6
Oophorectomy[c]				
Complete	7	25	0.5	0.2–1.3
Partial	10	13	1.2	0.4–3.4
Tonsillectomy[c]	95	149	1.3	0.8–2.0
Adenoidectomy[c]	41	86	0.7	0.3–1.4
Family history of:[d]				
Any cancer	83	143	1.1	0.7–1.7
Thyroid cancer	4	1	5.2	0.2–544
Breast cancer	17	25	1.2	0.6–2.6
Renal cancer	3	0	—[e]	0.7[f]
Regular use of:[g]				
Diuretics	14	21	1.2	0.5–2.7
Antihistamines	11	26	0.6	0.2–1.4
Antibiotics	8	21	0.7	0.2–1.7
Steroids	3	6	0.6	0.1–3.4
High blood pressure medicine	20	27	1.2	0.6–2.6
Ever use of medications for:				
Nausea (excluding pregnancy)	15	42	0.6	0.3–1.2
Severe diarrhea	20	42	0.7	0.3–1.3
Sleeping	21	41	0.9	0.5–1.7

[a] Drugs started within 2 yr of date of thyroid cancer diagnosis among cases and equivalent date for the controls were excluded.
[b] Adjusted for age, sex, prior radiotherapy to the head and neck, thyroid nodules, and goiter. Referent category taken as those individuals not exposed to variable of interest.
[c] Excludes surgeries within 2 yr of date of thyroid cancer diagnosis among cases and equivalent time for controls.
[d] Family members include parents, siblings, grandparents, and children.
[e] — = undefined.
[f] Upper limit undefined.
[g] Daily use for at least 3 mo, or off and on for at least 3 yr.

TABLE 7.—*Risk of thyroid cancer, by relative weight as measured by body mass index (BMI)*

Age[a]	BMI[b]	Male			Female		
		No. of cases	No. of controls	OR[c]	No. of cases	No. of controls	OR[c]
18 yr	I (low)	17	15	1.0	28	52	1.0
	II	13	19	0.4	23	54	0.7
	III	10	21	0.6	24	55	0.7
	IV (high)	10	21	0.5	33	46	1.5
Adult	I (low)	17	15	1.0	25	55	1.0
	II	8	23	0.3	28	52	1.3
	III	13	19	0.8	27	50	1.3
	IV (high)	12	19	0.6	29	50	1.5

[a] Wt at age 18 and/or ht information was not obtained for 1 female case and 2 female controls nor current weight for 2 female controls.
[b] BMI=wt/ht^2 (*47*). For adolescent females, the BMI ranged from 13.4 to 32.2, and from 16.2 to 40.8 for adult females. For adolescent males, the BMI ranged from 16.3 to 35.5, and from 20.4 to 38.1 for adult males.
[c] Adjusted for age, sex, prior radiotherapy to the head and neck, thyroid nodules, and goiter.

mostly due to a fourfold risk of medullary carcinoma (table 11). Source of drinking water (community vs. well) was similar for cases and controls (table 12).

Other Factors

Demographic variables did not appear to be important indicators for thyroid cancer in either males or females (table 12), However, persons whose parents were born in Italy had a twofold risk, whereas those of English descent were at significantly low risk. Jewish ethnicity was not significantly related to risk of thyroid cancer. No occupational associations were detected, including work exposures to radiation or jobs reflecting high SES. Neither alcohol intake nor cigarette smoking was related to the risk of thyroid cancer.

MLR Analysis

Variables entered into an MLR analysis included age, sex, radiotherapy, thyroid nodules, goiter, and vitamin D. For women, parity and miscarriage also were included (table 13). The OR for the major risk factors for thyroid cancer did not differ appreciably from those identified from the stratified analyses, although the OR associated with parity decreased from 2.2 to 1.4.

DISCUSSION

Radiation

Radiotherapy for past medical conditions of the head and neck was associated with a threefold risk of thyroid cancer. Although persons with thyroid cancer might have better recall of radiation exposure than do controls, we believe this potential bias is unlikely. In an attempt to address this issue, we asked respondents when they learned about their past radiation exposure. Only 3 of 19 cases had learned of their past exposure to radiotherapy within 3 years of thyroid cancer diagnosis. Exclusion of these 3 cases lowered the overall risk only slightly. It also is unlikely that exposed individuals were under closer medical surveillance than nonirradiated subjects, since the proportion of occult thyroid cancer (less than 1 cm) was similar for cases who received or did not receive past radiotherapy (24 and 19%, respectively). In a recent case-control study (6) conducted in Washington State, the risk of thyroid cancer was 19.8 when the physician discovered the tumor and 14.5 when the patient found the tumor. This finding would suggest that although close medical supervision may account for some of the excess risk, a high risk is still seen among women who detected their own tumor.

The proportion of thyroid cancers attributable to radiation decreased with birth cohort. This is consistent with the declining use of radiation treatment for benign head and neck conditions in the 1950's (2) and with the prediction by Pottern et al. (36) that thyroid cancer incidence should continue to decrease in Connecticut among persons born after 1950. We confirmed other observations indicating that x-irradiation is a strong factor for both papillary and follicular cancer (3, 4, 6), that the risk of radiogenic thyroid cancer is inversely related to age at radiation exposure (*3*), and that risk remains elevated for more than 40 years after exposure (2). We could not, however, confirm the exceptionally high risk associated with radiotherapy reported by McTiernan et al. (6) (OR= 16.5 as compared to 2.8 in our study). The higher risk for radiotherapy in the Washington study might reflect true differences in exposure or reporting frequencies (20% of the cases and 1.5% of the controls in Washington reported prior radiotherapy as compared to 12% and 4.3%, respectively, in Connecticut).

Although based on small numbers, parity appeared to potentate the radiation risk among women exposed during childhood. A similar observation was made in the study of Marshall Islanders exposed to radioactive fallout from a nuclear weapons test (*1*) and might result from the thyroid proliferation associated with the increase of TSH released during pregnancy (21, 37). The increase of TSH and thyroid glandular proliferation also may contribute to the high rates of thyroid cancer associated with childhood exposures to radiation (8).

Thyroid Disease

A high risk of thyroid cancer was observed among patients with a history of thyroid nodules or goiter, in agreement with two previous thyroid cancer case–control studies of females (6, 23). Although the mechanisms are unclear, this observation is consistent with experimental studies indicating that chronic iodine-deficient diets may lead to thyroid cancer through stages, including intense follicular hyperplasia, hypertrophy, and nodular and adenoma formation (7, 8). It is noteworthy that in areas of the world where goiter is endemic, the incidence of thyroid cancer is usually elevated (9). Correlation studies, however, are not entirely clear on the association of thyroid cancer with endemic goiter or with dietary iodine. Some endemic areas for goiter, such as Colombia, have high rates of thyroid cancer (9), but certain areas without endemic goiter, such as Iceland, also have high rates (38). It has been postulated that iodine-deficient diets are associated with goiter and the follicular type of thyroid cancer, whereas iodine-rich diets predispose to the papillary type of thyroid cancer (28). Although the

TABLE 8.—*Female risk of thyroid cancer associated with hormonal and reproductive factors, by age at diagnosis*

Reproductive factor[a]	Age at diagnosis, yr[b,c]: <35			35–79			All ages OR
	Cases (n=38)	Controls (n=85)	OR	Cases (n=71)	Controls (n=123)	OR	
Age at menarche, yr							
≤11[r]	5	21	1.0	10	19	1.0	1.0
12	8	20	1.5	17	31	0.8	1.0
13	14	24	2.1	24	30	1.1	1.4
14	11	20	2.0[d]	18	43	0.6	1.0
Menses							
Regular[r]	31	70	1.0	64	103	1.0	1.0
Irregular	7	15	0.8	7	20	0.6	0.7
Fertility problem							
No[r]	27	64	1.0	54	92	1.0	1.0
Yes	7	12	1.5	14	25	0.9	1.1
Pregnancy outcome							
Never pregnant[r]	10	39	1.0	6	16	1.0	1.0
Livebirth, ever	25	38	2.2	62	104	1.3	1.8
Miscarriage, ever	13	6	9.3[e]	23	37	1.4	3.3
Abortion, ever	2	8	0.9	4	3	2.5	1.4
Pregnant at interview	1	4	0.9	0	0	0.0	0.9
Stillbirth	0	0	0.0	4	4	1.9	1.9
No. of pregnancies							
0[r]	10	39	1.0	6	16	1.0	1.0
1	6	9	2.6	9	8	2.7	2.6
2	7	20	1.2	15	27	1.3	1.2
≥3	15	17	2.8[f]		72	1.3	1.9
No. of livebirths							
0[r]	13	47	1.0	9	19	1.0	1.0
1	8	15	1.9	13	16	2.1	2.0
2	14	16	2.5	24	29	1.5	2.0
≥3	3	7	1.6[g]	25	59	0.7	0.9
Age at first birth							
<20[r]	1	4	1.0	9	11	1.0	1.0
20–24	10	19	2.3	29	49	0.6	0.8
25–29	8	9	1.4	7	20	0.3	0.5
≥30	0	1	0.0	9	8	1.7	1.7
Lactation							
Never[r]	22	58	1.0	45	76	1.0	1.0
Ever	16	27	1.6	26	47	0.8	1.1
Age at menopause							
<40[r]	4	8	—	6	16	1.0	1.0
40–44	0	0	—	6	10	1.5	1.5
45–49	0	0	—	18	22	1.9	1.9
≥50	0	0	—	13	27	1.0	1.0

[a] r = referent category.
[b] Total No. of subjects varies due to missing data.
[c] ORs adjusted for age, sex, prior radiotherapy to the head and neck, thyroid nodules, and goiter.
[d] P (trend) = .14.
[e] Lower 95% CI >1.0.
[f] P (trend) = .05.
[g] P (trend) = .06.

TABLE 9.—*Risk of thyroid cancer, by hormone use among females*

Hormone	Age at diagnosis, yr						All ages OR
	<35			35–79			
	Cases (n=38)	Controls (n=85)	OR	Cases (n=71)	Controls (n=123)	OR	
Fertility drug	1	3	0.8	1	2	0.3	0.6
Diethylstilbestrol	0	0	0.0	1	5	0.3	0.3
Oral contraceptives for birth control	29	50	1.8	16	38	0.5	0.8
Oral contraceptives used for other reason	7	14	1.1	3	8	0.7	0.9
Menopausal estrogens	0	1	0.0	8	23	0.5	0.5
Other estrogens for gynecologic problems	2	1	3.6	4	4	1.8	2.2
Lactation suppressant	20	25	1.8	28	55	0.7	0.9
Any estrogen use[b]	35	66	2.4	44	83	0.7	0.9
Other drug use for gynecologic problems	3	4	1.7	2	7	0.2	0.6

[a] Adjusted for age, parity, prior radiotherapy to the head and neck. thyroid nodules, and goiter.
[b] Assuming all lactation suppressants were estrogens.

numbers were small, a history of goiter in our study did not preferentially increase the risk of follicular cancer, In addition, frequent consumption of shellfish, a rich source of dietary iodine, was associated with follicular rather than papillary carcinoma, which would have been expected on the basis of geographic correlations *(16)*.

In a retrospective study such as ours, recall bias of past thyroid disease among the cases cannot be discounted, especially since we did not attempt to verify these diagnoses of benign conditions. It is also possible that persons with thyroid nodules and goiter are under close medical surveillance for signs suggesting thyroid cancer. Access to medical care possibly could distort the association of thyroid cancer with nodules and goiter if differences existed between cases and controls. Thyroid cancers are often slow growing and asymptomatic, and it is possible that persons who seek medical care frequently might be more likely to have both their benign and malignant tumors detected than might individuals who rarely visit a physician or clinic. This possibility, however, seems unlikely in our study, inasmuch as we were unable to identify any differences between cases and controls in a wide range of indicators of medical care utilization, such as radiographic examinations and drug prescriptions. Furthermore, hypothyroidism and hyperthyroidism were not overrepresented among the cases, and it would thus seem im-

TABLE 10.—*Risk of thyroid cancer associated with past food consumption*

Food Item	OR[a], by frequency of consumption			Chi for trend	P-value[b]
	Infrequent[c]	Moderate[d]	Frequent[e]		
Milk	1.00	1.76	1.25	0.45	.33
Bread	1.00[f]		0.36	−1.57	.06
Salt	1.00	1.45	1.08	0.36	.36
Fish					
Shellfish[g]	1.00	0.73	1.77	0.14	.45
Saltwater	1.00	0.93	1.46	0.70	.24
Freshwater	1.00	0.41	1.91	−0.62	.27
Vegetables					
Cabbage[h]	1.00	0.77	0.79	−1.09	.14
Brussels sprouts[h]	1.00	0.73	0.72	−1.12	.13
Cauliflower[h]	1.00	0.95	0.77	−0.56	.29
Broccoli[h]	1.00	0.92	0.79	−0.85	.20
Goitrogens combined	1.00	1.00	0.77	−0.96	.17
Potatoes	1.00	0.59	0.51	−0.93	.18
Meat					
Chicken	1.00	0.59	0.64	−1.00	.16
Beef	1.00[f]		0.74	−0.93	.18

[a] Adjusted for age, sex, prior radiotherapy to the head and neck, thyroid nodules, and goiter.
[b] One-sided test.
[c] Infrequent = never or a few times a year. Referent category.
[d] Moderate = few times a month.
[e] Frequent = few times a week or daily.
[f] There were too few persons in the infrequent category to evaluate, so their data were combined with those in the moderate category,
[g] For follicular carcinoma. the risks were 1.00, 1.24, 3.77, respectively, and the P-value for trend = .09.
[h] Goitrogen.

TABLE 11.—*Risk of thyroid cancer associated with taking vitamin and mineral supplements regularly*[a]

Vitamin-mineral supplementation	No. of cases	No. of controls	OR[b]	95% CI
Never used	53	116	1.0[r]	
Multiple vitamins	106	167	1.4	0.9–2.1
With iron	58	117	0.6	0.9–2.2
Without iron	50	83	1.1	0.7–1.9
Vitamin A	32	40	1.7	0.8–3.6
Vitamin B complex	45	67	1.4	0.7–2.5
Vitamin C	66	104	1.5	0.9–2.6
Vitamin D	30	32	1.8	1.0–3.3[c]
Vitamin E	43	72	1.1	0.6–2.1
Calcium pills	35	54	1.2	0.6–2.4[d]
Zinc	17	35	0.9	0.4–2.2
Magnesium	12	27	0.8	0.3–2.3
Iron	45	63	1.6	0.8–3.0
Other	12	18	1.1	0.3–3.4

[a] "Regularly" was defined as every day for at least 3 mo, or off and on over a period of at least 3 yr.
[b] Adjusted for age, sex, prior radiotherapy to the head and neck, thyroid nodules, and goiter. r = referent category: those individuals who never took any specific vitamin or mineral regularly.
[c] Among medullary cancers, 4 were users, 5 were nonusers; OR = 4.3 (95% CI = 0.6–26).
[d] Among medullary cancers, 3 were users, 6 were nonusers; OR = 0.40 (95% CI = 0.02–3.9).

probable that diagnostic or recall bias would be associated only with goiter and nodules. Finally, since it is often difficult to distinguish between goitrous and neoplastic nodules, especially in high-risk areas, one could argue that thyroid cancer might actually be underdiagnosed among persons with enlarged thyroids.

Diet

The inverse association between thyroid cancer and the consumption of specific vegetables was surprising, particularly since 4 of the 5 vegetables studied contain thioglucosides that may be degraded to form goitrogens. In large quantities, goitrogens cause thyroid cancer in laboratory animals by blocking iodine uptake and the synthesis of thyroid hormones, thus causing the pituitary gland to increase TSH secretion. Cruciferous vegetables, however, also contain indole components, isothiocyanates, and phenols that may actually inhibit the development of certain cancers (39). Our dietary findings should be interpreted cautiously, since subjects were asked about only a small sample of foods and broad ranges of consumption. In addition, one-sided statistical tests were presented to indicate the positive or negative direction of the trends with increased consumption, and the level of "significance" becomes slightly less impressive when the P-values are doubled for two-sided tests. Future studies of thyroid cancer should include a more extensive evaluation of diet and nutritional status.

Regular use of vitamin D but not calcium supplements was significantly associated with thyroid cancer, especially medullary carcinoma, a tumor of the calcitonin-secreting C-cells. Although C-cell production of calcitonin is influenced by serum calcium levels, studies of laboratory animals have shown that dietary calcium does not increase the incidence of medullary-like tumors, whereas vitamin D increases both calcitonin production and a precursor lesion called C-cell hyperplasia (*16,40*). Thus the increased risk of medullary thyroid cancer associated with vitamin D intake deserves further study.

Reproductive Variables

Among women under age 35 years, risk factors included history of miscarriage and parity. Since TSH is a suspected thyroid cancer promoter (8, *16*) whose production increases during puberty and pregnancy (21, 37), these reproductive factors may contribute to the etiology of thyroid cancer. A history of pregnancy was associated with an elevated risk of thyroid cancer in two other recent studies (13, 21, 41). Our increased risk associated with miscarriage among younger women is consistent with the findings reported by Preston-Martin et al. (*13*). Although we found no statistically significant relationship between thyroid cancer and the use of oral contraceptives or lactation suppressants among younger women, the ORS were above unity and were consistent with those found by McTiernan et al. (*21*) and Preston-Martin et al. (*13*). However, it also should be noted that among women over age 35 years in our study, ORS below unity were seen.

Drugs

Several medications have been suggested as possible risk factors for thyroid cancer in epidemiologic surveys, including pentobarbital, diphenoxylate, dicyclomine, griseofulvin, bisacodyl, and senna (22). In animal studies, thyroid tumor development has been enhanced by administration of phenobarbital (42) and spironolactone (43). In our study, phenobarbital was taken by only 1 case and 1 control, and diphenoxylate (lomotil), used to control diarrhea, was taken by 8 cases and 20 controls (OR =0.7). However, spironolactone, a diuretic, was associated with a fourfold risk of borderline significance.

TABLE 12.—*Risk of thyroid cancer associated with demographic and other factors*

Variable	No. of cases[a]	No. of controls[a]	OR[b]	95% CI
Race				
White	152	277	1.00[r]	
Nonwhite	7	8	1.20	0.3–4.3
Religion[c]				
Protestant	49	110	1.00[r]	
Catholic	98	155	1.46	0.9–2.4
Jewish	8	11	1.70	0.5–5.8
Other	4	8	1.15	0.2–5.3
Ethnicity[d]				
German	4	8	1.3	0.3–6.3
Irish	1	3	0.8	0.03–11
Russian	4	3	1.3	0.1–13
Italian	20	20	2.1	0.8–6.1
English	0	7	0.0	0.0–0.9
Marital status				
Ever married	151	257	1.00[r]	
Never married	8	27	0.66	0.3–1.6
Education (grade)				
1–8	16	28	1.00[r]	
9–12	68	125	1.03	0.5–2.3
>12	74	130	0.92	0.4–2.1
SES[e]				
Low	30	67	1.00[r]	
Middle	60	89	1.40	0.8–2.6
High	66	114	1.14	0.6–2.1
Occupational exposure to radiation				
No	156	270	1.0[r]	
Yes	5	14	0.7	0.2–2.2
Residence				
Urban	60	105	1.00[r]	
Suburban	59	108	1.04	0.6–1.8
Rural	38	67	1.09	0.6–1.9
Place of birth				
United States	142	252	1.00[r]	
Other	17	32	1.10	0.6–2.2
Source of drinking water				
Community	118	224	1.00[r]	
Well	36	52	1.37	0.8–2.4
Tobacco product				
Nontobacco users	64	104	1.0[r]	
Cigarettes only	78	157	0.9	0.5–1.4
Cigars ever	9	12	1.6	0.3–7.9
Pipes ever	12	20	1.4	0.3–6.1
Alcohol use[f]				
Non-user	87	127	1.0[r]	
Any beer consumption	37	81	0.7	0.4–1.3
Any wine consumption	56	109	0.8	0.5–1.3
Any hard liquor	59	94	0.9	0.6–1.5

[a] Total No. of subjects varies due to missing data.
[b] Adjusted for age, sex, prior radiotherapy to the head and neck, thyroid nodules, and goiter. r = referent group.
[c] Also adjusted for Italian ancestry.
[d] Referent group includes persons with both parents born in the United States.
[e] Based on usual occupation. For homemakers, occupation of husband was used. Students are not included (2 cases, 13 controls).
[f] One or more alcoholic beverages consumed per week.

Other Factors

We found no significant relationship between thyroid cancer and previously suggested risk factors, such as Jewish ethnicity (2, 27), drinking water sources (9), tonsillectomy, allergy, various skin disorders such as psoriasis (17), or previous breast cancer (*15*, 41). However, we did confirm the higher risk associated with obesity among women (21, 41) and among persons with a family history of thyroid cancer (21).

Although familial occurrences are characteristic of medullary carcinoma (23), the familial tendency in our survey was confined to patients with the papillary type of cancer, reported previously only in a few clinical reports (24–26). Also noteworthy is the occurrence of renal cancer among first-degree relatives, particularly in view of the tendency for these particular cancers to develop as multiple primaries in individuals with thyroid cancer (44). Although not statistically significant, the association with surgery for benign breast disease is provocative in light of reports clinking breast and thyroid cancers (15, 41) and the observation in laboratory animals that diets low in iodine increase susceptibility to breast carcinogenesis (45). The high risk of thyroid cancer among persons of Italian ancestry and the low risk associated with English ancestry are difficult to explain and may just be chance events.

Methodologic Issues

Our findings should be interpreted cautiously in light of methodologic concerns: *a)* The overall response rate in the control group was only 62%, *b)* multiple comparisons were made so that some significant findings may arise by chance alone, c) the study size was comparatively small due to the rarity of thyroid cancer, and *d)* only the papillary and follicular types of thyroid cancer had sufficient numbers for risk factor evaluation, with few cases of medullary or anaplastic cancer occurring among those interviewed. The exclusion of 37 deceased cases from the study resulted in an underrepresentation of malignant lymphoma, medullary, and anaplastic thyroid cancers that have higher case fatality rates.

Nevertheless, our case-control interview study had several methodologic advantages. It was population based, and a pathology review was conducted on 97% of the cases. Also, selection of controls over age 65 from HCFA files of Medicare recipients enabled us to identify a representative sample of older persons. An unbiased sample would have been difficult or impossible to locate with the use of random digit-dialing techniques, since so many of the elderly are institutionalized and do not have private telephones (46).

Conclusions

In this case-control study, radiation exposure to the head and neck, especially during childhood, was found to increase the risk of thyroid cancer, with about 9% of all cases attributed to this exposure. With the reduction in use of radiation therapy for benign conditions, the proportion of radiogenic cancers is likely to decrease in the future. Persons with thyroid nodules (PAR = 17%) and goiter (PAR = 4%) were also prone to thyroid cancer, although these associations may be partly influenced by closer medical attention. The role of certain reproductive variables (miscarriage and parity) among younger women with thyroid cancer suggests a promotional effect of endogenous hormones, including TSH, and may help explain why parity seemed to potentate the radiation risks following childhood exposures. Since the causes of most thyroid cancer are yet to be discovered, the clues to other risk factors suggested by our study should be pursued.

TABLE 13.—*Risk of thyroid cancer associated with various risk factors, by MLR*

Risk factor	Adjusted OR[a]	MLR OR[b]	95% CI of MLR
Any radiotherapy to head or neck	2.8	2.6	1.2–5.9
Thyroid nodules	33.3	28.0	3.6–216
Goiter	5.6	3.8	0.7–21
Vitamin D	2.0	1.6	0.9–2.9
Multiparity[c]	2.0	1.4	0.5–3.4
Miscarriage[c]	9.3	5.0	1.4–18

[a] OR from previous stratified analysis, adjusted for age, sex, prior radiotherapy to head and neck, goiter, and thyroid nodules.
[b] Adjusted for age and sex.
[c] Females under age 35.

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